

1990 Application # _____

TOBACCO-RELATED DISEASE RESEARCH PROGRAM
University of California
RESEARCH AWARD APPLICATION

Check one:

☒ New Application
☐ Renewal

Circle Duration of proposed project:
 (1) (2) (3) years

Amount requested for
 1990-91: _____

Title of Research Project (do not exceed 60 spaces)

ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENT

Principal Investigator:

Ronald E. Rasmussen, Ph.D.

Associate Adjunct Professor

Name (first, last, degree(s))

Position/Title

Mailing address of Principal Investigator:

Ronald E. Rasmussen, PhD
 Community and Environmental Medicine
 California College of Medicine
 University of California, Irvine
 Irvine, CA 92717

RECEIVED

MAR 01 1990

Ans'd. *L.P. J.E.D.*

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Applicant Institution**Mailing Address of Official signing for Applicant Organization**

Olivia Nastri, Assistant Manager, Contracts and Grants

Name

Title

University of California, Irvine, CA 92717

Address

City

State

Zip Code

Verifications:

Signature Barth H. Korman Date 16 February 1990

Signature	Date	Name	Title
<i>Olivia Nastri</i>	2/27/90	OLIVIA NASTRI, CONTRACTS & GRANTS	MANAGER

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University of California
Tobacco-Related Disease Research Program

Budget

Year: 2 (7/1/91-6/30/92)

(Please submit a separate budget page for any subsequent years)

1) Personnel (list all professional and support personnel to be associated with the project and paid by the project)

<u>Name</u>	<u>Title of Position</u>	<u>% Time on Project</u>	<u>Salary Requested</u>	<u>Benefits</u>	<u>Total</u>
Rasmussen, R.E.	Assoc.Adj.Prof.	50%			
Phalen, R.F.	Professor	10%			
Bhalla, D.K.	Assoc.Prof.In-Res.	10%		REDACTED	
Bucher-Evans, S.	Stf.Res.Assoc.III	25%			
Mannix, R.	Stf.Res.Assoc.III	15%			
Daniels, D.	Sen.Animal Tech.	15%		REDACTED	
Brooks, K.	Admin.Asst.II	25%			
To Be Named	Stf.Res.Assoc.I	50%			

Total (All Personnel): \$ REDACTED

2) Supplies and Expenses (list general categories)

Animals and chemicals, \$17,490; radioactive and toxic waste disposal, \$3,710; equipment repair/maintenance, service contracts, \$4,452; office supplies, telephone, copy service, \$2,226; publication costs, \$1,325; and Sub-contract: T.R. McClure, \$5,300 /per year for histological analysis.

Total (All Supplies and Expenses): \$ 34,503

3) Equipment

Total Equipment: \$ 0

4) Domestic Travel

Total Travel: \$ 1,590

Total Requested for This Project Year
For Project Operation: \$ 166,311

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University of California
Tobacco-Related Disease Research Program

Budget continued

Year: 2 (7/1/91-6/30/92)

5) Indirect Costs (University of California and California State University
applicants may not apply for indirect costs)

Total indirect costs: \$ 0

Total requested for This
Project Year for Project
Operations plus Indirect
Costs: \$ 166,311

University of California
Tobacco-Related Disease Research Program

Budget

Year: 3 (7/1/92-6/30/93)

(Please submit a separate budget page for any subsequent years)

1) Personnel (list all professional and support personnel to be associated with the project and paid by the project)

<u>Name</u>	<u>Title of Position</u>	<u>% Time on Project</u>	<u>Salary Requested</u>	<u>Benefits</u>	<u>Total</u>
Rasmussen, R.E.	Assoc.Adj.Prof.	50%			
Phalen, R.F.	Professor	10%			
Bhalla, D.K.	Assoc.Prof.In-Res.	10%			
Bucher-Evans, S.	Stf.Res.Assoc.III	25%			
Mannix, R.	Stf.Res.Assoc.III	15%			
Daniels, D.	Sen.Animal Tech.	15%			
Brooks, K.	Admin.Asst.II	25%			
To Be Named	Stf.Res.Assoc.I	50%			

Total (All Personnel): \$ REDACTED

2) Supplies and Expenses (list general categories)

Animals and chemicals, \$18,539; radioactive and toxic waste disposal, \$3,933; equipment repair/maintenance, service contracts, \$4,719; office supplies, telephone, copy service, \$2,360; publication costs, \$1,404; and Sub-contract: T.R. McClure, \$5,618/per year for histological analysis.

Total (All Supplies and Expenses): \$ 36,573

3) Equipment

Total Equipment: \$ 0

4) Domestic Travel

Total Travel: \$ 1,685

Total Requested for This Project Year
For Project Operation: \$ 177,902

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University of California
Tobacco-Related Disease Research Program

Budget continued

Year: 3 (7/1/92-6/30/93)

5) Indirect Costs (University of California and California State University
applicants may not apply for indirect costs)

Total indirect costs: \$ 0

Total requested for This
Project Year for Project
Operations plus Indirect
Costs: \$ 177,902

BUDGET JUSTIFICATION

Personnel:

Ronald E. Rasmussen, Ph.D., P.I., 50% Time. Dr. Rasmussen will have primary responsibility for supervising all phases of the project. He will also participate directly in conducting experiments, gathering data, analysis of results and preparation of reports and publications. This project will represent 50% of his research activity.

Robert F. Phalen, Ph.D., Co-Investigator, 10% Time, WOS. Although no salary is requested for Dr. Phalen, his participation is necessary in order to coordinate activity in this project with other ongoing work at the Air Pollution Health Effects Laboratory. In the third year of the project, when particle deposition and clearance studies are undertaken, he will be involved in the experimental procedures directly.

Deepak K. Bhalla, Ph.D., Co-investigator, 10% Time. Dr. Bhalla will be responsible for the electron microscopy activities in the project, particularly the identification of cell types, and detection of tissue damage at the ultrastructural level.

Richard Mannix, Chamber Technician, 15% Time. Mr. Mannix will have responsibility for maintaining the exposure system(s) used in this study. This includes scheduling of exposures, repair of equipment, generation and monitoring of experimental atmospheres, and animal handling during exposures. He is presently employed at the APHEL and has had several years direct experience in these activities.

Shirley Bucher, Histology Technician, 25% Time. Ms Bucher has had several years direct experience in preparation of tissues for microscopic examination. She will aid in fixation, embedding, sectioning, staining and other activities associated with preparation of lung tissue for analysis.

Debra Daniels, Senior Animal Technician, 15% Time. Ms Daniels will be responsible for the day-to-day care of the ferrets used in this study. She is certified by the AALAC. She is currently responsible for handling and care of ferrets at the APHEL.

Staff Research Associate I (To Be Named), 50% Time. This person will be engaged in the biochemically-oriented portions of the project, which will include aiding in animal exposures, sacrifice of animals, lung lavage and preparation of slides, extraction and radioactivity measurement of lung DNA, and preparation and reading of autoradiographs. This person will be under the supervision of Dr. Rasmussen.

Kathy Brooks, Administrative Assistant, 25% Time. Ms Brooks will be responsible for fiscal matters, record keeping, and ordering supplies and materials.

University of California
Tobacco-Related Disease Research program

Financial Support (for each Professional)

Year: 1990

Investigator: Deepak K. Bhalla, Ph.D. Co-investigator

Name

Title of Project

List all grants and contracts on which you are named as a participant (specify agency, project title, amount, duration, your role in the project, and percent of time spent on the project.)

NIH R01 ES03521-04. Mechanisms of air pollutant induced airway permeability.

Total Award: \$1,128,326. Total Project Period: 12/01/87 - 11/30/92. Principal Investigator 50% Time.

California Air Resources Board. Chronic Toxicity of Mixed Air Pollutants.

Total Award: \$398,835. Project Period: 04/01/89-06/30/90. Co-investigator, 25% Time.

Pending Applications (specify agency, project title, amount, duration, your role in the project, and percent of time spent on the project.)

NIH 1 R01 HL/ES 44523-01. Juvenile ferret lung: Toxicological model for children.

Total recommended award \$421,177. Project period: 04/01/90-03/31/93. Co-investigator 10% Time.

Does your ability to conduct and complete this proposed research depend upon the funding or approval of another contract, grant, or award of any kind? Please specify.

No.

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University of California
Tobacco-Related Disease Research program

Financial Support (for each Professional)

Year: 1990

Investigator: Robert F. Phalen

Name

Title of Project

List all grants and contracts on which you are named as a participant (specify agency, project title, amount, duration, your role in the project, and percent of time spent on the project.)

NHLBI; Age & Body Size Factors in Inhaled Particle Deposition; \$760K; 7/88-6/92; Phalen, PI; 25%.

Cal. Dept. Hlth Svcs.; Airborne Dust Inhalation Exposure Assessments for Children & Adults; \$107K; 8/88-6/90; Phalen, PI; 15%.

Cal. Air Resources Board; Acidic Mixture Toxicology; \$123L; 12/89-2/91; Phalen, PI; 15%.

Pending Applications (specify agency, project title, amount, duration, your role in the project, and percent of time spent on the project.)

Cal. Air Resources Board; Toxicity of Chem. Constituents of PM10 in the S. Coast Air Basin of Calif; \$449K; 6/90-5/93; Bhalla, PI/Phalen 12%;

Nickel Producers Envir. Rsch. Assoc.; An Airway Model for the Laboratory Mouse; \$68K; 4/90-3/91; Phalen, PI, 5%.

Does your ability to conduct and complete this proposed research depend upon the funding or approval of another contract, grant, or award of any kind? Please specify.

No

BIOGRAPHICAL SKETCH

Ronald E. Rasmussen, Ph.D., Principal Investigator

Education

San Diego State University Life Science BS 1959
San Diego State University Biology MA 1962
Univ. of California, San Francisco, Ph.D. Microbiology, 1968

Professional Experience:

1977-present, Associate Adjunct Professor, UC Irvine
1975-77, Associate Research Physiologist, UC Irvine
1968-75, Assistant Research Physiologist, UC San Francisco
1965-68, Graduate student, UC San Francisco
1962-65, Research Scientist, NASA, Ames Res. Ctr, Mountain View, CA.

Professional Certification:

Diplomate, American Board of Toxicology, 1981.

Publications:

- Rasmussen, R.E., Boyd, C.H., Dansie, D.R., Kouri, R.E., and Henry, C.J., DNA replication and unscheduled DNA synthesis in lungs of mice exposed to cigarette smoke. *Cancer Res.* 41:2583-2588, 1981.
- McAllen, S.J., Chin, S.P., Phalen, R.F., and Rasmussen, R.E., The effect of in vivo ozone exposure on in vitro pulmonary alveolar macrophage mobility. *J. Toxicol. Environ. Health* 7:373-381, 1981.
- Rasmussen, R.E. and Crocker, T.T., Lung cells grown on cellulose membranes as an in vitro model of the respiratory epithelium. In: *Genotoxic Effects of Airborne Agents.*, R. Tice et al., eds., Plenum Press, New York, 1982.
- Rasmussen, R.E., In vitro systems for exposure of lung cells to NO₂ and ozone. *J. Toxicol. Environ. Health* 13:397-411, 1984.
- Rasmussen, R.E., Anderson, J., Kinkead, E.R., MacEwen, J.D., and Bruner, R.H., Carcinogenesis, benzo(a)pyrene metabolism and sister chromatid exchange in lungs of rats after intratracheal 3-methylcholanthrene. *J. Natl. Cancer Inst.* 73: 257-264, 1984.
- Rasmussen, R. E., Inhibition of DNA replication by ozone in Chinese hamster V79 cells. *J. Toxicol. Environ. Health* 17:119-128, 1986.
- Rasmussen, R.E., Dearden, L.C., Do, D.H., and Kim, T.S., Comparative cytotoxicity of naphthalene and its monomethyl and mononitro derivatives in the mouse lung. *J. Applied Toxicol.* 6:13-20, 1986.

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- Rasmussen, R.E., Metabolism and macromolecular binding of 1-nitronaphthalene in the mouse. *Toxicology* 41:233-247, 1986.
- Fong, A.T. and Rasmussen, R.E., DNA ethylation in hamster tissues during subchronic diethylnitrosamine administration and in the hamster trachea after acute diethylnitrosamine administration. *Carcinogenesis* 7:1457-1461, 1986.
- Fong, A.T. and Rasmussen, R.E., Formation and accumulation of O⁶-ethylguanine in DNA of enriched populations of Clara cells, alveolar type II cells, and macrophages of rats and hamsters treated with diethylnitrosamine or ethyl methanesulfonate. *Toxicology* 43:289-299, 1986.
- Rasmussen, R.E., Mutagenic activity of incense smoke in *Salmonella typhimurium*. *Bull. Environ. Contam. Toxicol.* 38:827-833, 1987.
- Berns, M.W., Liaw, L.H., Oliva, A., Andrews, J.J., Rasmussen, R.E., and Kimel, S., An acute light and electron microscopic study of ultraviolet 193 nm excimer laser corneal incisions. *Ophthalmology* 95:1422-1433, 1988.
- Rasmussen, R.E., and Bhalla, D.K., Transport across rat trachea in vitro after exposure to cytoskeleton active drugs in vitro or to ozone in vivo. *Exp. Lung res.* 15:253-268, 1989.
- Rasmussen, R.E., Devillez, G., and Smith, L.R., Influence of particulate trap oxidizers on emission of mutagenic compounds by diesel automobiles. *J. Applied Toxicol.* 9:159-168, 1989.
- Rasmussen, R.E., Hammer-Wilson, M., and Berns, M.W., Mutation and sister chromatid exchange induction in Chinese hamster ovary cells by pulsed excimer laser radiation at 193 nm and 308 nm and continuous UV radiation at 254 nm. *Photochem. Photobiol.* 49:413-418, 1989.
- Rasmussen, R.E., and Ullman, T.L., Effect of fuel properties on mutagenic activity in extracts of heavy duty diesel exhaust particulate. (Submitted for publication).
- Bhalla, D.K., Rasmussen, R.E., and Tjen, S., Interactive effects of O₃, cytochalasin D and vinblastine on transepithelial transport and cytoskeleton in rat airways. (Submitted for publication).

BIOGRAPHICAL SKETCH

Deepak K. Bhalla, Ph.D., Co-Investigator

Education:

Punjab University, Chandigarh, India, Honors School, B.Sc. 1968
Punjab University, Chandigarh, India, Honors School, M.Sc. 1969
Howard University, Washington, DC, Cell Biology, Ph.D., 1976
Harvard University, Boston, MA, Cell Biology, Post Doc, 1979

Professional Experience:

1989-present, Associate Professor in Residence, Community and Environmental Medicine, UC Irvine.
1982-1989, Assistant Adjunct Professor, Community and Environmental Medicine, UC Irvine.
1979-1982, Assistant Research Cell Biologist, Dept. of Medicine, University of California Medical Center, San Francisco, and Cell Biology Section, VA Medical Center, San Francisco, CA.
1976-1979, Postdoctoral fellow, Dept. of Pathology, Harvard Medical School, Boston, MA.
1971, Research Scholar, Dept. of Zoology, Punjab University, Chandigarh, India.

Publications:

- Bhalla, D.K., Braun, J., and Karnovsky, M.J., Lymphocyte surface and cytoplasmic changes associated with translational motility and spontaneous capping of Ig., J. Cell Sci. 39:31-44, 1979.
- Klausner, R.D., Bhalla, D.K., Dragsten, P., Hoover, R.L., and Karnovsky, M.J., Model for capping derived from inhibition of surface receptor capping by free fatty acids., Proc. Natl. Acad. Sci. U.S. 77:437-441, 1980.
- Hoover, R.L., Bhalla, D.K., Yanovich, S., Inbar, M., and Karnovsky, M.J., Effects of linoleic acid on capping, lectin mediated mitogenesis, surface antigen expression, and fluorescent polarization in lymphocytes and BHK cells., J. Cell Physiol. 103:399-406, 1980.
- Bhalla, D.K., Murakami, T., and Owen, R.L., Microcirculation of intestinal lymphoid follicles in rat Peyer's patches. Gastroenterology 81:481-491, 1981.
- Hoover, R.L., Fujiwara, K., Klausner, R.D., Bhalla, D.K., and Karnovsky, M.J., Effects of free fatty acid on the organization of cytoskeletal elements in lymphocytes. Mol. Cell. Biol. 1:939-948, 1981.
- Owen, R.L., and Bhalla, D.K., Lymphoreticular tissues and thymus. In: Biomedical Research Applications of Scanning Electron Microscopy, Vol. 3, G.M. Hodges and R.C. Hallows, eds., Academic Press, New York, pp. 79-169, 1983.

- Bhalla, D.K., and Owen, R.L., Migration of B and T lymphocytes to M cells in Peyer's patch follicle epithelium. An autoradiographic and immunocytochemical study in mice. *Cell. Immunol.* 81:105-115, 1983.
- Owen, R.L., and Bhalla, D.K., Cytochemical analysis of alkaline phosphatase, esterase, lectin, and anionic sites in rats and mouse Peyer's patch follicle epithelium., *Amer. J. Anat.* 168:199-212, 1983.
- Bhalla, D.K., Mannix, R.C., Kleinman, M.T., and Crocker, T.T., Relative permeability of nasal, tracheal, and bronchoalveolar mucosa to macromolecules in rats exposed to ozone. *J. Toxicol. Environ. Health* 17:269-283, 1986.
- Crocker, T.T., and Bhalla, D.K., Transport of macromolecules and particles at target sites for deposition of air pollutants., *Health Effects Institute Report* 3:15-57, 1986.
- Bhalla, D.K., and Crocker, T.T., Tracheal permeability in rats exposed to ozone: An electron microscopic and autoradiographic analysis of the transport pathway. *Amer. Rev. Resp. Disease* 134:572-579, 1986.
- Owen, R.L., Apple, R.T., and Bhalla, D.K., Morphometric and cytochemical analysis of lysosomes in rat Peyer's patch follicle epithelium: Their reduction in volume fraction and acid phosphatase content in M cells compared to adjacent enterocytes. *Anat. Record* 216:521-527, 1986.
- Bhalla, D.K., and Crocker, T.T., Pulmonary epithelial permeability in rats exposed to O₃. *J. Toxicol. Environ. Health* 21:73-87, 1987.
- Bhalla, D.K., Mannix, R.C., Lavan, S.M., Phalen, R.F., Kleinman, M.T., and Crocker, T.T., Tracheal and bronchoalveolar permeability in rats inhaling oxidant atmospheres during rest or exercise. *J. Toxicol. Environ. Health* 22:417-437, 1987.
- Bhalla, D.K., Lavan, S.M., and Crocker, T.T., Airway permeability in rats exposed to O₃ or treated with cytoskeleton destabilizing drugs. *Exp. Lung Res.* 14:501-525, 1988.
- Rasmussen, R.E., and Bhalla, D.K., Transport across rat trachea in vitro after exposure to cytoskeleton active drugs in vitro or to ozone in vivo., *Exp. Lung Res.* 15:253-268, 1989.
- Ling, K.Y., Bhalla, D.K., and Hollander, D., Mechanisms of carrageenan injury of IEC18 small intestinal epithelial cell monolayers. *Gastroenterology* (1990, In press).
- Mahavni, V., Bhalla, D.K., and Nguyen, T., A morphological analysis of damage to nasal epithelia in rats exposed to formaldehyde. *Scanning Microsc. International* (1990, In press).

BIOGRAPHICAL SKETCH

Robert F. Phalen, Ph.D., Co-Investigator

Education:

California State University, San Diego, Physics, BA, 1964
California State University, San Diego, Physics, MA, 1966
University of Rochester, Rochester, NY, Biophysics, Ph.D., 1971

Professional Experience

1984-present, Professor, Community and Environmental Medicine;
Director, Air Pollution Health Effects Laboratory, UC Irvine.
1978-84, Professor in Residence, Community and Environmental Medicine,
UC Irvine.
1974-1978, Assistant Adjunct Professor, Community and Environmental
Medicine, UC Irvine.
1972-1974, Research Associate, Aerosol Physics Dept., Lovelace Fdn.
for Medical Education and Research, Albuquerque, NM.
1970-1972, Summer Faculty, Biology Dept., Rochester Inst. of
Technology, Rochester, NY.
1966, Instructor, Physics Dept., Cal State San Diego, San Diego, CA.
1963-1966, Assistant to Radiation Safety Officer/Laboratory Teaching
Assistant, Physics Dept., Cal State San Diego, San Diego, CA
1962-1963, Engineering Aide, Advanced Systems Dept., General
Dynamics/Astronautics, San Diego, CA.

Selected Publications

- Phalen, R.F., Crocker, T.T., McClure, T.R., and Tyler, N.K., Effect of
ozone on mean linear intercept in the lung of young beagles.
J. Toxicol. Environ. Health 17:285-296, 1986.
- Phalen, R.F., Hinds, W.C., John, W., Liroy, P.J., Lippmann, M.,
McCawley, M.A., Raabe, O.G., Soderholm, S.C., and Stuart,
B.O., Rationale and recommendations for particle size-
selective sampling in the workplace., Appl. Ind. Hyg. 1:3-14,
1986.
- Stuart, B.O., Liroy, P.J., and Phalen, R.F., Particle size-selective
sampling in establishing threshold limit values., Appl. Ind.
Hyg. 1:138-144, 1986.
- Walters, R.B., Nordenstam, B.J., and Phalen, R.F., A generator for the
production of sulfuric acid coated diesel soot aerosols.,
Atmos. Environ. 22:17-23, 1988.
- Phalen, R.F., Stuart, B.O., and Liroy, P.J., Rationale for and
implications of particle size-selective air sampling. In:
Advances in Air Sampling, W. John, ed., Lewis Publications,
Inc., Chelsea, MI, 1988.

- Smith, C.M., Batcher, S., Catanzaro, A., Abraham, J.L., and Phalen, R.F., Sequence of bronchoalveolar lavage and histopathologic findings in rat lungs early in inhalation asbestos exposure., *J. Toxicol. Environ. Health* 20:147-162, 1987.
- Bhalla, D.K., Mannix, R.C., Lavan, S., Phalen, R.F., Kleinman, M.T., and Crocker, T.T., Tracheal and bronchoalveolar permeability changes in rats inhaling oxidant atmospheres during rest or exercise., *J. Toxicol. Environ. Health* 22:417-437, 1987.
- Prosad, S.B., Rao, S.V., Mannix, R.C., and Phalen, R.F., Effects of pollutant atmospheres on surface receptors of pulmonary macrophages., *J. Toxicol. Environ. Health* 24:385-402, 1988.
- Mautz, W.J., Kleinman, M.T., Phalen, R.F., and Crocker, T.T., Effects of exercise exposure on toxic interactions between inhaled oxidant and aldehyde air pollutants., *J. Toxicol. Environ. Health* 25:165-177, 1988.
- Kleinman, M.T., Phalen, R.F., Mautz, W.J., Mannix, R.C., McClure, T.R., and Crocker, T.T., Health effects of acid aerosols formed by atmospheric mixtures., *Environ. Health Perspectives* 79:137-145, 1989.
- Phalen, R.F., Oldham, M.J., Kleinman, M.T., and Crocker, T.T., Tracheobronchial deposition predictions for infants, children, and adolescents., *Ann. Occup. Hyg.* 32:11-21, 1988.
- Phalen, R.F., Oldham, M.J., and Mautz, W.J., Aerosol deposition in the nose as a function of body size., *Health Physics* (1989, In press).
- Phalen, R.F., and Prasad, S.B., Morphology of the respiratory tract. In: *Concepts in Inhalation Toxicology*. R.O. McClellan, and R.F. Henderson, eds., Hemisphere Publishing Co., New York, 1989.
- Kleinman, M.T., McClure, T.R., Mautz, W.J., Phalen, R.F., and Crocker, T.T., Effects of inhaled oxidant and acidic air pollutant combinations on nasal and tracheal tissues in exercising rats., *Ann. Occup. Hyg.* 32:239-245, 1988.
- Phalen, R.F., Hinds, W.C., John, W., Liou, P.J., Lippmann, M., McCawley, M.A., Raabe, O.G., Soderholm, S.C., and Stuart, B.O., Particle size-selective sampling in the workplace: Rational and recommended techniques., *Ann. Occup. Hyg.* 32:403-411, 1988.
- Oldham, M.J., Phalen, R.F., and Huxtable, R.F., Growth of the ferret tracheobronchial tree., *Lab. Animal Sci.* (1990, Submitted).

University of California
Tobacco-Related Disease Research Program

Relevance of the Project/Facilities Available

Discuss the relevance of your proposed research to tobacco-related diseases in the State of California and what impact your research might have on these diseases and the California population at risk.

Many children in California are exposed to Environmental Tobacco Smoke (ETS) from their earliest childhood until they leave home on their own. There is evidence that risks from ETS include increased susceptibility to respiratory disease and permanent lung damage. Cigarette smoking is a well known risk factor for lung disease, but the extent of risk for those breathing only ETS (children and nonsmokers) has not been firmly established. Work done in animals has employed "mainstream" tobacco smoke, i.e., smoke that has passed through the cigarette, and many of the toxic compounds present in "sidestream" smoke (smoke from the burning end of the cigarette) are filtered out. Consequently, the results of animal studies to date are of limited value in estimating the results of ETS exposure. The proposed studies will address directly the toxic effects and concentration-response relationships of ETS in the developing lung. The studies will use the ferret as an animal model because its lung structure resembles that of the human more than do the lungs of rats, mice, or hamsters. Hence, the damage produced by ETS in the ferret is expected to resemble that in the human. The main goal of this project is to determine the effect of ETS on the developing lung. The young ferret undergoes very rapid growth, from about 15 g at birth to as much as 1 kg at 20 weeks. The proposed experiments will expose ferrets to ETS during this period of rapid growth, and in this way the effects of ETS on lung development can be determined. An important point is that similar studies will be done in parallel in this laboratory with NO₂, a well-studied air pollutant gas known to produce lung damage. It will therefore be possible to compare directly the effects of ETS with those of NO₂ under the same laboratory conditions. The results of these studies will provide concentration-response data for ETS which can be used in estimating the risk to children.

Facilities and Resources (Describe the facilities and resources that are needed and are available for successfully carrying out the proposed research.)

SEE ATTACHED DESCRIPTION

Facilities and Resources

Laboratory: The Air Pollution Health Effects Laboratory (APHEL) was established in 1974 with the specific goal of basic research on the health effects of airborne particles, gases and vapors. The lab has 6 large ($>1\text{ m}^3$) inhalation chambers, 3 physiology laboratories, a histology laboratory, analytical chemistry lab, particle lab, radioisotope lab, lung casting and morphometry lab, in-house machine and electronic lab, and library, conference, and seminar areas. Additional laboratory space of approximately 900 sq ft in a separate building will be available for biochemical aspects of this project.

Animal Housing Facility at the APHEL is under the supervision of the campus veterinarian and complies with all relevant regulations. It is not a general-use facility, but is limited to only those animals used in experiments at the APHEL. The facility consists of 6 separate but adjoining rooms, each with its own HEPA filtered air supply, temperature and humidity controls. The arrangement is such that different species do not occupy or pass through each others living space. Atmospheres are scrubbed with charcoal and bacteriological filters to minimize contamination from external sources. Access is restricted to personnel specially trained in animal handling and who are supervised by an AALAC-certified animal technician. Gloves, masks and clean lab coats are worn by all persons entering the facility. Periodic inspection by governmental agencies ensures compliance with all pertinent regulations. Relevant to the proposed work, separate air-barrier housing for the ferrets has been provided. A new high-temperature cage washer has been installed in order to ensure sanitary housing.

Computer Facilities: Laboratory-interfaced PDP 11/10 with 2 disk drives, dual floppy disks, FORTRAN and FM tape. Five micro PCs with access to University computer facilities and the MEDLINE data base are in place. Installation of a high capacity modem and FAX facility have recently been completed.

Office: The APHEL has 10 separate offices for faculty and staff plus a central office for clerical and word processing. Fiscal records and purchasing are in the departmental office in a separate building.

Major Equipment: Four Rochester-type chambers, 2 APHEL-designed chambers, and nose-only exposure facilities for up to 50 animals simultaneously allow pollutant generation, characterization and animal exposure. Major equipment includes a gamma counter, an MT-6000 ultramicrotome equipped with a cryo sectioning unit, an "ultra-freeze" biological cryofixation unit, 2 Sorvall microtomes, an analytical balance, a Cahn Electrobalance, a Nikon fluorescence microscope, a digital image analyser interfaced with a Nikon light microscope, a Samdri critical point drying apparatus, and a Hummer VI vacuum metal coating unit for SEM. Scanning and transmission electron microscopes, a Balzers freeze fracture apparatus and dark rooms for photography are used in the Biological Sciences Building. A Tracor 300-sample scintillation spectrometer, Beckman Model L centrifuge, Sorvall RC2 centrifuge, and other small equipment are also available to this project.

2025794407

Equipment Needed: Two major items of equipment are needed for this project. A nose-only exposure manifold will be needed for exclusive use in this project. There is no similar equipment available at the APHEL. The current work load at the APHEL requires continuous use of exposure systems that might be adapted to this project. The manifold will become contaminated to some extent with tobacco tar, making it unsuitable for use with other airborne agents without extensive cleaning.

The second item of needed equipment is a cigarette smoking machine. We will attempt to obtain a previously owned machine, which would result in some savings. No such machine is available on this campus, and it is obviously vital for the proposed work.

2025794408

APPLICANT INSTITUTION PROFILE

Legal Name: The Regents of the University of California

Date of Incorporation: 1963

Type of Institution (Higher Ed; Hospital; etc.) Institution of Higher Education

Tax Exempt Status (IRS Code Number): 95-2226406

Annual Budget: \$ 366,165,000

Name of External Auditor: Peat, Marwick, Main & Co.

Date of Most Recent Audit: 9/89

Which Federal Agency approves your indirect cost rates? DHHS

What is the date of your latest indirect cost rate negotiation agreement? February 3, 1989

If your indirect cost rate is not federally approved, what is the basis for the rate proposed in your budget?

Business Officer with whom to negotiate award:

Name: Chary Bulaciak

Title: Administrative Analyst

Address: University of California

Telephone No.: (714) 856-4781

2025794409

1 RT 134

UNIVERSITY OF CALIFORNIA, IRVINE

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SANTA BARBARA • SANTA CRUZ

COLLEGE OF MEDICINE
DEPARTMENT OF COMMUNITY AND
ENVIRONMENTAL MEDICINE

IRVINE, CALIFORNIA 92717

July 12, 1991

Annette McCoubrey
UCTDRP
Office of the President
University of California
300 Lakeside Drive
12th Floor
Oakland, CA. 94612

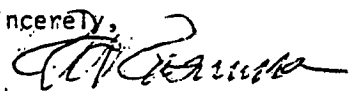
Re: RT-134 "ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENT"

Dear Ms McCoubrey:

Enclosed is a copy of the approved renewal for the use of ferrets in the above referenced grant.

Please call if you need further information.

Sincerely,


Ronald E. Rasmussen, Ph.D.
Adjunct Professor

2025794410

J RT 134

**RENEWAL TO APPROVED PROTOCOL
FOR USE OF LABORATORY ANIMALS IN RESEARCH**

ARC# 90-1100

TO: Ronald Rasmussen
Community and Environmental Medicine

RE: **ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENT**

Our records indicate that approval for use of laboratory animals in the above project expires 03/31/91. If you wish to continue and avoid a lapse in approval, please answer questions 1-7 below and return the completed form to the Research Committees Office. Please note: If you do not return this form by the project expiration date stated, your approval will automatically expire and you will be unable to order additional animals.

If you **DO NOT** wish to renew approval for this project, please sign & date on the line provided and return this form to the Research Committees Office, 115 Administration Bldg. _____

THIS FORM MUST BE TYPED AND ALL INFORMATION PROVIDED (insert N/A if non-applicable)

"SEE ATTACHED" is not an acceptable response. An attachment sheet may only be used once the space provided has been utilized.

1. BRIEF SUMMARY OF ORIGINAL APPROVED PROTOCOL:

Weanling ferrets will be exposed to dilute cigarette smoke for either a short period or repeatedly during development. The aim of the study is to determine effects of low concentrations of tobacco smoke on lung growth.

2. PROGRESS REPORT (Describe progress of study, observations made):

One group of 17 weanling ferrets have been exposed to dilute smoke. Analysis of lung and other tissues is in progress. No experimental results or conclusions are available at this time.

3. IF YOU WISH TO MAKE ANY CHANGES TO THE MOST RECENTLY APPROVED PROTOCOL PLEASE DESCRIBE (If none, state "none."):

We wish to use the adult female ferrets in studies of the effect of dilute tobacco smoke in the adult animal. These studies would be done after the kits were weaned or used in the approved experiments. The methods would be the same as in the currently approved protocols. No additional animals are requested.

4. NUMBER OF ANIMALS (PER SPECIES) ORIGINALLY REQUESTED 60 ferrets

***ACTUAL NUMBER USED SINCE LAST APPROVAL** 25 ferrets

***NUMBER OF ANIMALS TO BE USED DURING NEXT PERIOD** 60 ferrets

***If there is increase in number, please provide justification:**

2025794411

1 RT 134

5. LIST ANY CHANGES IN PERSONNEL ATTENDING THE ANIMALS (their responsibilities, P.L., CO P.L., Tech., Department, training and qualifications).

Add - Technician: Andrea Linden, Animal Technician
Community and Environmental Medicine

6. DESCRIBE ANY ADVERSE EFFECTS OBSERVED OR UNANTICIPATED PROBLEMS (If none, state "none"):

None

Our records show the following animals are approved for use on this protocol. If there is any discrepancy, please correct.

60 FERRETS

INVESTIGATOR'S ASSURANCE

The information given in response to the questions above is accurate and I understand that PRIOR TO INITIATING ANY CHANGES in my research protocol affecting the use and care of laboratory animals, APPROVAL OF THE ARC WILL BE OBTAINED.



Signature of Principal Investigator

13 Mar 91
Date

REAPPROVAL FOR USE OF LABORATORY ANIMALS IN THE ABOVE PROJECT IS GRANTED FROM 3/31/91 TO 3/31/92 (INCLUSIVE DATES)



Signature: Chair, ARC or designee

3/28/91
Date Approved

Return original form to Research Committees Office, 115 ADM

kr:newrenwl

2025794412

1 RT 134

5. LIST ANY CHANGES IN PERSONNEL ATTENDING THE ANIMALS (their responsibilities - P.I., CO P.I., Tech., Department, training and qualifications.

Add - Technician: Andrea Linden, Animal Technician
Community and Environmental Medicine

6. DESCRIBE ANY ADVERSE EFFECTS OBSERVED OR UNANTICIPATED PROBLEMS (If none, state "none"):

None

Our records show the following animals are approved for use on this protocol. If there is any discrepancy, please correct.

60 FERRETS

INVESTIGATOR'S ASSURANCE

The information given in response to the questions above is accurate and I understand that PRIOR TO INITIATING ANY CHANGES in my research protocol affecting the use and care of laboratory animals, APPROVAL OF THE ARC WILL BE OBTAINED.


Signature of Principal Investigator

13 Mar 91
Date

REAPPROVAL FOR USE OF LABORATORY ANIMALS IN THE ABOVE PROJECT IS GRANTED
FROM 3/31/91 TO 3/31/92 (INCLUSIVE DATES)


Signature: Chair, ARC or designee

3/28/91
Date Approved

Return original form to Research Committees Office, 115 ADM

kr:newrenwl

2025794413

1-RT 134
Puum**RENEWAL TO APPROVED PROTOCOL
FOR USE OF LABORATORY ANIMALS IN RESEARCH**

ARC# 90-1100

TO: Ronald Rasmussen
Community and Environmental Medicine

RE: ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENT

Our records indicate that approval for use of laboratory animals in the above project expires 03/31/91. If you wish to continue and avoid a lapse in approval, please answer questions 1-7 below and return the completed form to the Research Committees Office. Please note: If you do not return this form by the project expiration date stated, your approval will automatically expire and you will be unable to order additional animals.

If you **DO NOT** wish to renew approval for this project, please sign & date on the line provided and return this form to the Research Committees Office, 115 Administration Bldg. _____

THIS FORM MUST BE TYPED AND ALL INFORMATION PROVIDED (insert N/A if non-applicable)

"SEE ATTACHED" is not an acceptable response. An attachment sheet may only be used once the space provided has been utilized.

1. BRIEF SUMMARY OF ORIGINAL APPROVED PROTOCOL:

Weanling ferrets will be exposed to dilute cigarette smoke for either a short period or repeatedly during development. The aim of the study is to determine effects of low concentrations of tobacco smoke on lung growth.

2. PROGRESS REPORT (Describe progress of study, observations made):

One group of 17 weanling ferrets have been exposed to dilute smoke. Analysis of lung and other tissues is in progress. No experimental results or conclusions are available at this time.

3. IF YOU WISH TO MAKE ANY CHANGES TO THE MOST RECENTLY APPROVED PROTOCOL PLEASE DESCRIBE (If none, state "none."):

We wish to use the adult female ferrets in studies of the effect of dilute tobacco smoke in the adult animal. These studies would be done after the kits were weaned or used in the approved experiments. The methods would be the same as in the currently approved protocols. No additional animals are requested.

4. NUMBER OF ANIMALS (PER SPECIES) ORIGINALLY REQUESTED 60 ferrets***ACTUAL NUMBER USED SINCE LAST APPROVAL** 25 ferrets***NUMBER OF ANIMALS TO BE USED DURING NEXT PERIOD** 60 ferrets***If there is increase in number, please provide justification:**

2025794414

University of California, Irvine

FAX #: (714) 725-2094

FAX TRANSMISSION FORM

There are 3 pages in this transmittal (including this cover sheet).

FROM: Name: Rita Galvan Telephone: (714) 856-6068

Address:

Office of Contract & Grant Administration
University of California, Irvine
115 Administration Building
Irvine, CA 92717

TO: FAX #: 415 835-4750

Phone #:

Name:

Location:

Address:

Annette Ma Doubray
UC Tobacco Related Research Program
300 Lakeside Drive - 12th floor
Oakland, Calif. 94612

Delivery Instructions: (☒) Urgent (☐) Routine

Comments:

for Ronald Laumann request.
Regarding Grant # RT134
Renewal approval for 1992

FAX transmitted by: Rita

Date:

7/10/91

Time:

2:45

NOTE TO RECEIVER: If you do not receive the number of pages indicated, please call (714) 856-7106 immediately.

2025794415

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SANTA BARBARA • SANTA CRUZ

Tobacco-Related Disease Research Program
Office of the President
Vice President—Health Affairs
300 Lakeside Drive, 12th Floor
Oakland, CA 94612-3550
(415) 987-9870
FAX 835-4740

October 23, 1991

Olivia Nastri
University of California, Irvine
Office of Contracts & Grants
115 Administration Bldg
UC Irvine
Irvine, CA 92717

Dear Ms. Nastri:

The University of California Tobacco-Related Disease Research Program requires an annual fiscal report for every grant award. In accepting these awards you agreed to provide these reports as stipulated. Reports were due on September 30, 1991, and to date, we have not received them for the grant(s) referenced below.

<u>ID No.</u>	<u>Investigator</u>	<u>Project Title</u>
---------------	---------------------	----------------------

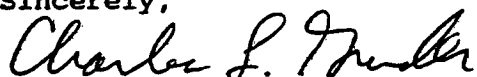
2025794416

✓ RT 134 Ronald E. Rasmussen

Environmental Tobacco Smoke &
Lung Development

Please write to explain this delay and inform us when we may expect the report(s).

Sincerely,



Charles L. Gruder, Ph.D.
Director

2025794417

UNIVERSITY OF CALIFORNIA
TOBACCO-RELATED DISEASE RESEARCH PROGRAM
PROGRESS REPORT

ABSTRACT OF RESEARCH RESULTS

AWARD # RT-134 AWARD PERIOD 07/01/90-06/30/91PRINCIPAL INVESTIGATOR Ronald E. Rasmussen, Ph.DINSTITUTION University of California, IrvineTITLE OF PROJECT ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENT

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The goal of this project is to determine the effects of environmental tobacco smoke (ETS) in the developing lung. The rationale for the study is that young children may be exposed to relatively high indoor concentrations of tobacco smoke and possibly other pollutants. An animal model, the juvenile ferret, is being used in this study. The lung of this species resembles that of the human more than do the lungs of other commonly used laboratory animals. The ferrets are being exposed to ETS acutely or chronically during development, and the effects on lung structure quantified by microscopy of tissue sections. In the first year of this study cigarette smoking machines, exposure apparatus and smoke generation and measurement methods were installed. Acute exposure dose-response experiments (1 hr/day, 3 days, 30-80 mg smoke particles/m³) with 4-week-old kits indicated no immediate severe effects. Total numbers of cells recovered in lung washings were slightly increased and microscopic examination indicated increased cell proliferation in the smoke exposed animals. Experiments involving longer exposure to higher smoke concentrations have been completed and tissue samples are being analyzed. Tentative conclusions are (1) the juvenile ferret tolerates the handling and smoke exposure methods very well and is a useful species for the study of effects of air pollutants in the lung; (2) acute effects of exposure to ETS are not severe, but they can be detected and quantified. The major goal for the second year will be to determine the effects of daily exposure to ETS during the period of development from 5 weeks to 20 weeks of age.

2025794418.A

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September 14, 1990

Dr. Ronald E. Rasmussen
University of California, Irvine
Community & Environmental Medicine
California College of Medicine
Irvine, California

Tobacco-Related Disease Research Program
Office of the President
Vice President—Health Affairs
2150 Shattuck Avenue
Suite 500A
Berkeley, California 94720
(415) 642-5220

Project: RT 134 - Environmental Tobacco Smoke & Lung Development

Dear Dr. Rasmussen:

Enclosed please find a compilation of the reviewer's comments and study section discussion of the above referenced application to the University of California Tobacco-Related Disease Research Program (TRDRP). Also included is a summary of your annual budget for the term of your award and a brief explanation of any changes which were made to the budget.

All applications were considered and ranked within their study section. The percentile rank given provides information on where this application placed in its study section; the highest ranked application in the study section received a percentile ranking of 100. The ranking is based on the average of the scores given to the application by all the study section members at the time the application was discussed during the study section meeting. The lowest percentile ranking which received funding in the Pulmonary study section was 76.

In addition to the summary, we have enclosed a copy of the abstracts of the projects which were funded in the Pulmonary study section. The names of the study section members are also listed in this publication.

If you have any additional questions concerning the review process or your grant, please contact Annette McCoubrey at (415) 642-7014. Once again, congratulations on your award.

Sincerely,

Paul Torrens, M.D., M.P.H.
Interim Director

Enclosures

RT 134

2025794418

UNIVERSITY OF CALIFORNIA
TOBACCO-RELATED DISEASE RESEARCH PROGRAM
PROGRESS REPORT

OTHER SUPPORT

AWARD # RT-134 AWARD PERIOD 07/01/90-06/30/91
PRINCIPAL INVESTIGATOR Ronald E. Rasmussen, Ph.D.
TITLE OF PROJECT ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENT

NHLBI/NIH 1 RO1 HL/ES 44523. Juvenile ferret lung: Toxicological model for children. 01 July 90 through 30 June 93. Total direct cost: \$386019. 50% Time. This project is a study of the effects of NO₂ on the developing lung in the ferret. Although the same species and methods are used, the project does not overlap with the present application because a different toxicant is being studied.

Applications Pending.

California Air Resources Board. "Studies to Determine the Long-Term Health Effects of Acidic Atmospheres". (██████████, P.I.). Budget and start date under negotiation. 5% Time. This project involves chronic exposure of rats to mixtures of ozone and HNO₂. Dr. Rasmussen's activities would include advising on lung pathology and morphometric analyses. It is unrelated to the present application. When and if the project is begun, Dr. Rasmussen's commitment to currently funded projects will be reduced proportionately.

NIEHS. "QUANTITATIVE MORPHOMETRY OF METAL TOXICITY IN THE LUNG". P.I.: R. E. Rasmussen, PhD. 30% Time. Inclusive dates: 04/01/92-03/31/95. Approx. total direct costs: \$450,000. The goal of this project is to determine the dose-response relationships for metal-induced alterations in the developing and young adult rat lung. Cadmium will be administered by inhalation of a sized particulate prepared in a pilot-scale rotary kiln incinerator. If this project is funded, the P.I.'s commitment to currently funded projects will be reduced proportionately.

2025794419

UNIVERSITY OF CALIFORNIA
TOBACCO-RELATED DISEASE RESEARCH PROGRAM
PROGRESS REPORT

CHANGES IN KEY PERSONNEL

AWARD # RT-134 AWARD PERIOD 07/01/90-06/30/91PRINCIPAL INVESTIGATOR Ronald E. Rasmussen, Ph.D.TITLE OF PROJECT ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENTNO CHANGES!

1. Person named in the grant application:

Name	Title	% Time
------	-------	--------

Changed to:

Name	Title	% Time
------	-------	--------

2. Person named in the grant application:

Name	Title	% Time
------	-------	--------

Changed to:

Name	Title	% Time
------	-------	--------

3. Person named in the grant application:

Name	Title	% Time
------	-------	--------

Changed to:

Name	Title	% Time
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Use additional pages if necessary

2025794420

UNIVERSITY OF CALIFORNIA
TOBACCO-RELATED DISEASE RESEARCH PROGRAM
PROGRESS REPORT

PUBLICATIONS

AWARD # RT-134 AWARD PERIOD 07/01/90-06/30/90
PRINCIPAL INVESTIGATOR Ronald E. Rasmussen, Ph.D.
TITLE OF PROJECT ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENT

List publications which acknowledge support from this program; listings should include the author(s), title, journal or book name, year of publication, volume, and inclusive page numbers. Attach reprints.

None

2025794421

UNIVERSITY OF CALIFORNIA
TOBACCO-RELATED DISEASE RESEARCH PROGRAM

TOBACCO FUNDING FROM OTHER SOURCES

AWARD # RT-134 AWARD PERIOD 07/01/90-06/30/91
PRINCIPAL INVESTIGATOR Ronald E. Rasmussen, Ph.D.
INSTITUTION University of California, Irvine
TITLE OF PROJECT ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENT

- A. Is any of your current tobacco-related work supported by sources other than the TRDRP?

Yes No X

- B. Approximate State funding for tobacco-related disease research (from sources other than TRDRP) for fiscal year 1990-91.

\$ None

- C. Approximate Federal Funding for tobacco-related disease research for fiscal year 1990-91.

\$ None

Ronald E. Rasmussen 25 June 91
Signature of Private Investigator Date

Olivia Nastri 6/27/91
Signature of Grant Officer Date

OLIVIA NASTRI, MANAGER
CONTRACTS & GRANTS

2025794422

UNIVERSITY OF CALIFORNIA
TOBACCO-RELATED DISEASE RESEARCH PROGRAM

ANIMAL SUBJECT USE REPORT

AWARD # RT-134 AWARD PERIOD 07/01/90-06/30/91
PRINCIPAL INVESTIGATOR Ronald E. Rasmussen, Ph.D.
INSTITUTION University of California, Irvine
TITLE OF PROJECT ENVIRONMENTAL TOBACCO SMOKE AND LUNG DEVELOPMENT

(1) Animal Use Information

A. Will you use animals in your TRDRP research project?

Yes X

No

B. If yes:

Species of animals to be used

Number/Year

Ferret

Approx. 80

(2) Use of Animal Alternatives

A. In your opinion, will your project utilize any alternatives that reduce, replace, or refine the use of animals?

Yes

No X

B. Describe briefly the animal alternatives to be used in your project.

Ronald E. Rasmussen
Signature of Principal Investigator

25 June 91
Date

Olivia Nistri
Signature of Grant Officer

6/23/91
Date

OLIVIA NISTRI, MANAGER
CONTRACTS & GRANTS

2025794423

FINANCIAL SUPPORT

Investigator: Ronald E. Rasmussen, PhD, Principal Investigator

Active Support:

NIEHS 5R01 ES03521. Mechanisms of air pollutant induced airway permeability. (P.I.: [REDACTED]). Annual direct costs approx. \$130,000. Inclusive dates 2/1/85-11/30/92. Co-investigator, 10% Time.

[REDACTED] Project # [REDACTED]. A standard human DNA repository for studying cancer. [REDACTED] P.I.). Total Direct Cost \$20,000. Inclusive Dates, 7/1/89-6/30/90. Co-investigator, 20% Time.

California Department of Health Services (No number). A pilot study of risk factors in childhood cancer. [REDACTED] P.I.). Total Direct Cost, \$24,000. Inclusive dates, 11/1/89-6/30/90. Co-investigator, 20% time.

Pending Support:

NIH 1 R01 HL/ES 44523-01. Juvenile Fefret Lung: Toxicological Model for Children. (R. Rasmussen, P.I.). Annual Direct Costs approx. \$135,000. Inclusive dates: 07/01/90-06/30/93. 50% time. This application has been approved, but funding is uncertain at this time.

NIH 1 R01 ES 05435-01. Genetic/Environmental Study of Childhood Tumors. [REDACTED] P.I.). Annual Direct Costs approx. \$550,000. Inclusive dates: 07/01/90-06/30/94. Co-investigator, 50% Time.

NIH 1 R01 CA 48970-01A2. A Case-Control Study of Small Cell Carcinoma of the Lung. [REDACTED] P.I.). Annual Direct Costs approx. \$300,000. Inclusive dates: 07/01/90-06/30/95. Co-investigator, 75% time.

Dependence of this proposed research on other grants:

Conduct and completion of the work proposed in the present application does not depend on the funding or approval of any other grant or contract.

2025794425

Relationship of Current and Pending Support to This Application

Current Support:

NIEHS 5R01 ES03521. The aim of this project is to describe the mechanisms of action of ozone on the permeability of the airway epithelium to other pollutants. It uses the rat as an animal model and also rat lung cells in culture. It is unrelated to the work proposed in this application.

~~XXXXXXXXXX~~ Project #XXXX. In this project peripheral blood samples are being collected from families, the lymphocytes separated, and preserved for future examination of DNA restriction fragment length polymorphisms. The project is unrelated to the present application.

California Dept. of Health Services Pilot Study. This project is a preliminary study of childhood cancer cases in Orange County, CA. The goal is to discover risk factors associated with the appearance of childhood cancer. Blood samples are collected from cancer case, their parents and siblings, and also from control families. Cultured lymphocytes are examined for their sensitivity to chromosome breakage in vitro. A questionnaire and environmental survey are used to disclose possible risks in the home or familial factors. The project is unrelated to the present application.

Pending Support:

NIH 1 R01 HL/ES 44523-01. This project is resembles that proposed in the present application, with the major exception that the air pollutant is nitrogen dioxide (NO₂). The exposure methods are similar, as are the endpoints for determining the effects of the pollutant. This project is considered to be complementary to the work proposed in the present application, since it will allow comparison of the effects of a well-studied pollutant gas with those of environmental tobacco smoke. However, the two projects are independent, and can be done separately without additional resources above those requested in the budget.

NIH 1 R01 ES 05435-01. This application is for a continuation of the above study of childhood cancers, and is unrelated to the present application.

NIH 1 R01 CA 48970-01A2. This project is aimed at determining risk factors specific to small cell lung cancer. Some of the laboratory methods to be used are the same as those in the present application, but the project is unrelated in terms of its specific aims.

2025794426

Equipment:

Nose-only Exposure Manifold, with accessory equipment, In-Tox Model 03-100 or equivalent \$12,000. This manifold will be specially designed and constructed by In-Tox corporation specifically for use with tobacco smoke. Equivalent equipment does not exist at the APHEL, or on the UC Irvine campus. The manifold will be a dual plenum, two-sided design, with 15 exposure ports on each side. One side will be used exclusively for smoke exposure, while the other will be for clean air. The requested equipment will be installed at the APHEL and would be dedicated to this project, thus ensuring timely completion of the proposed studies. The cost is based on an estimate from In-Tox Corp.

"Walton" Cigarette smoke generating machine, or equivalent, \$4,500. The Walton cigarette smoking machine is a well-proven design that has been used in many studies. For the proposed work the machine will need to be modified to provide both mainstream and sidestream smoke. The cost is based on previous prices from Process and Instruments Corp., Brooklyn, NY.

Seven-Stage Cascade Impactor, \$850. This device is required for characterization of the tobacco smoke particulate fraction. The cost is based on estimates from In-Tox Corp.

Supplies and Materials: Total \$32,550.

Animals, Including original cost, shipping and quarantine, \$6,000. This figure is based on current prices of approximately \$120 for each animal, plus shipping. This amount will provide for 50 animals.
Food and bedding, \$2500. This amount is based on current experience at the APHEL.

Radioisotopes, \$1,200. In the first year, this amount will be used for [³H]-thymidine, and will provide approximately 100 mCi.

Misc. chemicals, fixatives and EM supplies, \$2,500. This will provide funds for the fixation and preparation of lung tissue for analysis. Also included will be photoemulsion for autoradiography and scintillation cocktail. Research cigarettes will be purchased from the University of Kentucky.

Exposure system hardware, including animal exposure tubes, \$3,000. For exposure of juvenile ferrets, it will be necessary to fabricate new exposure tubes. Also, replacement hardware (tubing, valves, etc.) will be needed to maintain the exposure system.

Glassware and plasticware, \$1,300. These items will be used in studies of DNA replication, and will include pipets, and vials for scintillation counting.

Radioactive and Toxic Waste Disposal, \$3,500. This expense is crucial to the project. The University requires that funds be specifically requested for this activity. The amount is based on the estimated waste to be generated during the year.

Equipment repair and maintenance contracts, \$4,200. This represents a share of expenses for a scintillation spectrometer, centrifuges, gamma counter, and for repair of major items including a cage washer.

Telephone, library, office supplies and copy services, \$2,100. This represents a share of the indicated expenses, and is based on current costs.

Publication, reprints, page charges, and preparation of illustrations for publication of research results, \$1,250.

Subcontract: Thomas R. McClure, MS, Histology Specialist. Mr. McClure will provide assistance in histological analysis and direct participation in morphometric analysis. A subcontract for his services will be arranged, consistent with University regulations. The estimated cost of services is \$5,000 per year.

Travel: One trip for PI or Co-Investigator to Soc. of Toxicology meeting, Miami, FL, 1991, \$1,500.

* Supplies and materials expenses are expected to increase by 6% for years 2 and 3.

** Where applicable a 5%-7.2% increase is included for merit increases. A 5% cost-of-living increase is added each January. Benefit rates for academic and staff positions are 22.5% and 28.5% respectively with a 1% increase for years 2 and 3.

2025794428

University of California
Tobacco-Related Disease Research Program

Budget

Year: 1 (7/1/90-6/30/91)

(Please submit a separate budget page for any subsequent years)

1) Personnel (list all professional and support personnel to be associated with the project and paid by the project)

Name	Title of Position	% Time on Project	Salary Requested	Benefits	Total
Rasmussen, R.E.	Assoc.Adj.Prof.	50%			
Phalen, R.F.	Professor	10%			
Bhalla, D.K.	Assoc.Prof.In-Res.	10%			
Bucher-Evans, S.	Stf.Res.Assoc.III	25%		REDACTED	
Mannix, R.	Stf.Res.Assoc.III	15%			
Daniels, D.	Sen.Animal Tech.	15%			
Brooks, K.	Admin.Asst.II	25%			
To Be Named	Stf.Res.Assoc.I	50%			REDACTED

Total (All Personnel): REDACTED

2) Supplies and Expenses (list general categories)

Animals and chemicals, \$16,500; radioactive and toxic waste disposal, \$3,500; equipment repair/maintenance, service contracts, \$4,200; office supplies, telephone, copy service, \$2,100; publication costs, \$1,250; and Sub-contract: T.R. McClure, \$5,000/per year for histological analysis.

Total (All Supplies and Expenses): \$ 32,550

3) Equipment

Nose-only exposure apparatus, with ancillary equipment, specially designed for smoke exposure, \$12,000; seven-stage cascade impactor for smoke particle characterization, \$850; "Walton" cigarette smoke generating machine (or equivalent), \$4,500

Total Equipment: \$ 17,350

4) Domestic Travel

Total Travel: \$ 1,500

Total Requested for This Project Year
For Project Operation: \$ 169,293

University of California
Tobacco-Related Disease Research Program

Budget continued

Year: 1 (7/1/90 - 6/30/91)

5) Indirect Costs (University of California and California State University
applicants may not apply for indirect costs)

Total indirect costs: \$ -0-

Total requested for This
Project Year for Project
Operations plus Indirect
Costs: \$ 169,293

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